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New Phenotype Definition of Attention Deficit Hyperactivity Disorder in Relatives for Genetic Analyses

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The goal of the present investigation was to create a phenotype definition in relatives of probands that reflects a more genetic form of attention deficit hyperactivity disorder (ADHD). Logistic regression was applied to the first-degree relatives of ADHD and normal control probands to create a quantitative phenotype that combined information across psychiatric, cognitive, and demographic domains. Models were run separately in mothers, fathers, sisters, and brothers. Although there was some overlap between the variables retained in each model, no two models had exactly the same variables. Our results suggest that the use of fitted logits may be valuable as a potential index of caseness. Since different characteristics were included in different groups of relatives, our results suggest that gender and generation may moderate the expression of ADHD.

KEY WORDS: psychiatric morbidity, familial transmission, logistic regression

INTRODUCTION

Family studies of attention deficit hyperactivity disorder (ADHD) have found that the relatives of ADHD children are at high risk for ADHD [Biederman et al., 1990, 1991a,b; Cantwell, 1972; Faraone et al., 1992; Faraone and Santangelo, 1992; Lahey et al., 1989; Mannuzza and Gittelman, 1984; Morrison, 1980; Morrison and Stewart, 1971; Schachar and Wachsmuth, 1990; Stewart et al., 1980; Welner et al., 1977]. Although familial transmission may be of genetic or environmental origin, it is believed that genes play an important role in the familial transmission of ADHD based on data from half-sibling, twin, adoption, and segregation analysis studies [Cantwell, 1975; Deutsch et al., 1990; Faraone and Santangelo, 1992; Goodman and Stevenson, 1989a,b; Lopez, 1965; Morrison and Stewart, 1973; Rutter et al., 1963; Safer, 1973; Torgersen and Kringlen, 1978; Willerman, 1973]. If a single major gene does exist, misclassification could make it difficult, if not impossible, to detect with linkage or association studies.

In this investigation we were interested in classifying ADHD into categories that discriminated between genetic and nongenetic subtypes of the disorder. This is what Tsuang et al. [1993] referred to as "psychiatric genetic nosology." This approach does not suggest that such a nosology will be useful for clinicians or that it should replace DSM-III-R. What it does imply is that psychiatric genetics need not rely on diagnostic constructs for other purposes [Tsuang et al., 1993]. A psychiatric genetic nosology needs to address the key measurement issues in psychiatric genetics. Of primary concern is the group of false-positives. This refers to a group of subjects who are classified as having ADHD but are incorrectly classified as having a genetic subform of the illness (i.e., subjects who have the phenotype but not the genotype). These false-positives are of critical concern in genetic studies since they may lead to reduced statistical power and attenuated evidence for genetic linkage [Chen et al., 1992; Tsuang et al., 1993]. False-negatives (i.e., subjects who do not express the phenotype but have the genotype) are also of concern in genetic analyses, but to a lesser extent since they do not have the same impact on statistical power.

Typically, the phenotype definition for ADHD has been based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification system, which treats diagnoses as dichotomous traits [American Psychiatric Association, 1987; Tsuang et al., 1993]. In many cases, however, such a dichotomy comes about after examining several variables on an individual, and

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then applying a rule as to who is affected and who is unaffected. This dichotomization process can yield considerable loss of information and misclassification. Ott [1991] developed an approach that addressed these issues. His scheme is based on a measure of certainty that an individual is truly affected and assigns weights according to the probability that the subject is affected. These weights can be the predictions made by mathematical models of disease expression [Tsuang et al., 1993]. In a linkage analysis, these weights can be used to quantify the penetrance of each genotype for diagnoses made with varying degrees of certainty [Ott, 1991].

Therefore, differences in demographic and clinical features in relatives of ADHD probands and relatives of normal controls may be combined to create Ott's measure of certainty that would weight the contribution of individual relatives in a linkage analysis by the chance that they have the genetic form of ADHD. If any one of these characteristics were examined individually it might not be highly predictive, whereas the combination of a number of characteristics into a composite profile might yield considerable predictive ability [Blacker et al., 1993; Blacker and Tsuang, 1993].

Specific characteristics that may be of particular use in the new phenotype definition in relatives are gender and comorbidity status. Gender is relevant in that it may moderate the phenotypic expression of ADHD. For example, males may be more hyperactive and impulsive while females may be more inattentive and have more internalizing problems. This gender difference is evidenced by ADHD being 6–9 times more prevalent in males than females [Anderson et al., 1987; Bird et al., 1988; Safer and Krager, 1988].

Comorbidity status may be another important characteristic to examine in the new phenotype definition, since it is believed that ADHD with various comorbid psychiatric disorders represents a group of conditions with different etiological risk factors rather than a single homogeneous clinical entity. More specifically, it is believed that ADHD with conduct disorder may represent a distinct genetic subtype of ADHD [Faraone et al., 1991], that ADHD and major depression share common familial etiologic factors [Biederman et al., 1991b], and that ADHD and anxiety disorders are etiologically independent [Biederman et al., 1991a].

Modeled after recent work by Blacker and Tsuang [1993] and by Faraone et al. [1995], the present work uses logistic regression to discriminate relatives of ADHD probands from relatives of normal controls. As discussed in Subjects and Methods, this allowed us to create a quantitative phenotype definition in relatives that combined information across psychiatric, cognitive, and demographic domains.

SUBJECTS AND METHODS

Subjects

We analyzed data from a family-genetic study of ADHD that has been described previously [Biederman et al., 1992]. Briefly, this study selected two groups of index children: 140 ADHD probands and 120 normal controls. These groups had 454 and 368 first-degree biological relatives, respectively. The number of mothers, fathers, sisters, and brothers in each of these groups is delineated in Table I. We sampled families through Caucasian, non-Hispanic male probands between ages 6–17 years. Potential probands were excluded if they had been adopted, or if their nuclear family was not available for study. We also excluded probands if they had major sensorimotor handicaps (e.g., paralysis, deafness, or blindness), psychosis, autism, or a full-scale IQ <80. Subjects from the lowest socioeconomic class (SES VI) [Hollingshead, 1975] were excluded to minimize the potential confounding of social adversity. All ADHD probands met DSM-III-R diagnostic criteria for current ADHD at time of clinical referral. Two independent sources provided the index children, as described elsewhere [Biederman et al., 1992]. A three-stage ascertainment procedure was used to select all probands regardless of their source of referral [i.e., Massachusetts General Hospital (MGH) or Harvard Community Health Plan (HCHP)]. In each case, sampling was based on consecutive referrals.

For purposes of this investigation, only those parents who were interviewed directly about themselves were included in the analysis. This led to the exclusion of 42 (16%) fathers and 2 (1%) mothers. Moreover, relatives with incomplete data were also excluded. Six (2%) mothers, 10 (4%) fathers, 17 (11%) sisters, and 22 (14%) brothers were excluded for this reason. Thus, data on 252 (97%) mothers, 207 (80%) fathers, 131 (89%) sisters, and 133 (86%) brothers were used in the analysis. Table I provides a breakdown of the number of available subjects by whether they were related to an ADHD proband or to a normal control proband.

Procedures

All diagnostic assessments were made using DSM-III-R-based structured interviews. Psychiatric assessments of probands and siblings were made with the Kiddie SADS-E (Epidemiologic Version) [Orvaschel and Puig-Antich, 1987]. Diagnoses were based on indepen-

TABLE I. Number of First-Degree Biological Relatives of Probands

	Relatives of ADHD probands		Relatives of normal control probands	
Type of relative	Total number (N = 454)	Number included (% of total)	Total number (N = 368)	Number included (% of total)
Mothers	140	136 (97%)	120	116 (97%)
Fathers	140	111 (79%)	119	96 (81%)
Sisters	81	68 (84%)	67	63 (94%)
Brothers	93	78 (84%)	62	55 (89%)

dent interviews with mothers and direct interviews of probands and siblings, except for children below age 12 years, who were not directly interviewed. Diagnostic assessments of parents were based on direct interviews with each parent, using the Structured Clinical Interview for DSM-III-R (SCID) [Spitzer and Williams, 1986].

All assessments were made by raters who were blind to proband diagnosis (ADHD or control) and ascertainment site [MGH or Health Maintenance Organization (HMO)]. Mothers' interviews about their children were sequenced after the direct interview with the mother about herself had been completed. Different raters conducted the direct interviews of siblings and the indirect interviews with mothers about their children. Interview data were collected on all siblings in both ADHD and control families. All parents signed a written consent form for participation in the study.

Interviews were conducted by five raters with undergraduate degrees in psychology who had been trained to high levels of interrater reliability. Kappa coefficients of agreement were computed between raters and three experienced, board-certified child and adult psychiatrists who listened to audiotaped interviews made by the raters. A kappa of 1.0 was obtained for ADHD (95% confidence interval, 0.8–1.0).

Diagnoses were considered positive if, based on interview results, DSM-III-R criteria were unequivocally met. All diagnostic uncertainties were resolved by a committee of four board-certified child and adult psychiatrists who were blind to the subject's ascertainment group, ascertainment site, all data collected from other family members, and all nondiagnostic data (e.g., cognitive functioning). Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. For children older than 12 years, symptom data from direct and indirect interviews were combined by considering a symptom positive if it were endorsed in either interview. Children below age 12 years were not directly interviewed for a number of reasons: they have limited language capabilities, are often unable to map events over time, and have limited abilities with abstract concepts. Given these shortcomings, there is a real issue as to whether the child's self-perceptions, memories, emotions, and reported behavior can be reliably assessed through self-report. Studies on the use of interview techniques among children under age 12 years show that they only understand between 28–38% of the questions [Breton et al., 1995], that their replies are not reliable [Achenbach et al., 1987], and that their parents tend to be more reliable informants [Edelbrock et al., 1986; Gutterman et al., 1987].

In parents and siblings, symptom scores were created corresponding to ADHD and the various psychiatric disorders that are frequently comorbid with ADHD (e.g., conduct disorder, major depression, and anxiety disorders). That is, for each of these diagnostic categories, the number of symptoms endorsed was summed to give an index of severity, instead of using the dichotomous DSM-III-R classification system.

Academic achievement was assessed with the Arithmetic Subtest of the Wide Range Achievement Test (WRAT-R) [Jastak and Jastak, 1985] and the Gilmore Oral Reading Test [Gilmore and Gilmore, 1968]. Intellectual functioning was assessed with the vocabulary, block design, digit span, and digit symbol subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) [Wechsler, 1974]. A total cognitive score was created by standardizing each of the above-mentioned cognitive variables and summing them. This cognitive score was then itself standardized to increase the interpretability of this measure.

Data Analysis

Univariate comparisons were conducted to assess the ability of individual variables to discriminate relatives of ADHD probands from relatives of normal controls. Chi-square tests were used for categorical variables, two sample t-tests were used for approximately normal continuous or ordinal variables, and Wilcoxon tests were used for continuous or ordinal variables with skewed distributions.

In an attempt to define a phenotype of ADHD that is highly prevalent among relatives of ADHD probands but rare in the relatives of normal controls, logistic regression was applied to the first-degree relatives of ADHD and normal control probands. Let P denote the probability of being a first-degree relative of an ADHD proband. The logarithm of the odds, $\log[P/(1 - P)]$, is called the logit of P. Logistic regression models the logit as a linear function of the explanatory variables, which included the symptom scores of various psychiatric disorders, the cognitive summary functioning score, socioeconomic status, and past and current global assessment of functioning scores. All explanatory variables were submitted to a forward stepwise logistic regression using a significance level to enter or stay in the model of 0.05. At each step, the improvement in χ^2-test was used to check whether the variable entered at that step significantly improved the log-likelihood. Parameter estimates were obtained using maximum likelihood. After the last step, the hypothesis that the logistic model fit the data adequately was tested with the Hosmer-Lemeshow test [Hosmer and Lemeshow, 1989].

Once the final logistic regression models were determined in each group of relatives, the equivalence of these models was tested. This was done by using identical variables in each of the four models (a variable was included if it was retained in any of the stepwise logistic regression models). The log-likelihoods from these four individual models were then summed and compared with the log-likelihood from the model looking at all relatives at once. The difference in log-likelihoods was multiplied by two and evaluated using a χ^2-test.

After estimates of the coefficients were obtained, an estimate of the probability of being a relative of an ADHD proband was calculated for each relative in the study as follows:

$$\hat{P} = \frac{e^{\{\text{logit}(\hat{P})\}}}{[1 + e^{\{\text{logit}(\hat{P})\}}]}$$

These predicted probabilities provided a quantitative index of how likely a subject was to be a relative of an

ADHD proband based on the relative's profile of characteristics as retained in the logistic regression model.

An important issue to consider when working with family data is that family members are not statistically independent of one another due to shared cultural and/or genetic factors. Although this dependency is not likely to have a large effect on parameter estimates it can influence statistical testing. Dependency between subjects results in decreased variability which, in turn, can yield underestimates of significance levels (i.e., smaller *P* values). To control for this, four different logistic models were run for each type of relative of probands: one for mothers, one for fathers, one for sisters, and one for brothers. This attempt to eliminate dependency also helped address the issues of gender and generational effects, which may have considerable impact on ADHD family data. However, it was still possible that there were some related family members in the two models looking at siblings (i.e., a proband could have had two or more same-sex siblings). Since our primary aim was the separation of relatives of ADHD and normal control probands rather than hypothesis-testing, we ignored this lack of independence in the models using sisters and brothers. However, the magnitude of this problem should not be great, since the number of brothers and sisters in these families was not large. More specifically, in those families with brothers, 84% had only 1 brother, 13% had 2 brothers, and 3% had 3 brothers. Similarly, in those families that had sisters, 80% had only 1 sister, 17% had 2 sisters, and 3% had 3 sisters.

RESULTS

Table II presents the associations between group status (i.e., being a relative of an ADHD proband vs. a relative of a normal control proband) and each of the

TABLE IIa. Univariate Analyses in Mothers (N = 252)

	Mothers of ADHD probands (N = 136)	Mothers of normal controls (N = 116)	*P* value
Extra help in school	25% (34)	9% (11)	0.002
Repeated grade in school	20% (27)	5% (6)	0.0006
Special class in school	1% (1)	0% (0)	1.0
	Mean ± SD	Mean ± SD	
ADHD symptom score	2.4 ± 3.5	0.72 ± 1.5	0.0001
Conduct disorder symptom score	0.45 ± 0.86	0.20 ± 0.51	0.005
Major depression symptom score	3.6 ± 3.3	2.0 ± 2.9	0.0001
Separation anxiety symptom score	0.50 ± 1.2	0.36 ± 0.77	0.10
Panic disorder symptom score	1.5 ± 1.5	0.43 ± 1.4	0.0002
Antisocial personality disorder symptom score	1.6 ± 1.1	1.3 ± 0.63	0.006
Generalized anxiety disorder symptom score	2.3 ± 3.8	0.5 ± 1.9	0.0001
Cognitive summary score	−1.2 ± 3.7	0.65 ± 2.9	0.0001
Current global assessment of functioning score	69.3 ± 10.1	75.9 ± 7.0	0.0001
Past global assessment of functioning score	57.9 ± 13.2	66.9 ± 11.1	0.0001
Socioeconomic status	1.8 ± 0.83	1.5 ± 0.67	0.0007

TABLE IIb. Univariate Analyses in Fathers (N = 207)

	Fathers of ADHD probands (N = 111)	Fathers of normal controls (N = 96)	*P* value
Extra help in school	26% (29)	15% (14)	0.06
Repeated grade in school	23% (25)	21% (22)	0.87
Special class in school	3% (3)	2% (2)	1.0
	Mean ± SD	Mean ± SD	
ADHD symptom score	3.8 ± 3.8	1.7 ± 2.4	0.0001
Conduct disorder symptom score	1.2 ± 1.5	0.76 ± 1.5	0.006
Major depression symptom score	3.0 ± 2.9	1.8 ± 2.6	0.003
Separation anxiety symptom score	0.39 ± 0.75	0.19 ± 0.53	0.005
Panic disorder symptom score	0.52 ± 1.7	0.44 ± 1.5	0.60
Antisocial personality disorder symptom score	2.1 ± 1.3	1.6 ± 0.93	0.005
Generalized anxiety disorder symptom score	1.4 ± 3.2	0.98 ± 2.2	0.71
Cognitive summary score	−0.29 ± 4.7	1.3 ± 3.7	0.01
Current global assessment of functioning score	68.2 ± 10.2	72.6 ± 8.0	0.001
Past global assessment of functioning score	56.5 ± 12.5	62.9 ± 11.9	0.0001
Socioeconomic status	1.6 ± 0.79	1.4 ± 0.59	0.06

TABLE IIc. Univariate Analyses in Sisters (N = 131)

	Sisters of ADHD probands (N = 68)	Sisters of normal controls (N = 63)	*P* value
Extra help in school	35% (24)	22% (14)	0.12
Repeated grade in school	0% (0)	0% (0)	N/A
Special class in school	3% (2)	10% (8)	0.17
	Mean ± SD	Mean ± SD	
ADHD symptom score	2.9 ± 3.8	1.5 ± 2.6	0.04
Agoraphobia symptom score	0.21 ± 0.59	0.13 ± 0.42	0.66
Conduct disorder symptom score	0.59 ± 1.2	0.22 ± 0.63	0.03
Major depression symptom score	2.1 ± 3.1	2.2 ± 3.0	0.87
Separation anxiety symptom score	1.1 ± 1.5	0.78 ± 1.0	0.23
Simple phobia symptom score	1.8 ± 2.0	1.2 ± 1.8	0.06
Social phobia symptom score	1.3 ± 1.9	0.71 ± 1.4	0.08
Overanxious symptom score	1.6 ± 1.9	1.4 ± 1.8	0.32
Panic disorder symptom score	0.53 ± 1.5	0.55 ± 1.6	0.71
Cognitive summary score	−0.29 ± 3.3	0.44 ± 3.0	0.19
Current global assessment of functioning score	70.3 ± 11.0	72.3 ± 8.7	0.22
Past global assessment of functioning score	63.8 ± 12.5	66.3 ± 11.4	0.19
Socioeconomic status	1.7 ± 0.80	1.5 ± 0.70	0.23

TABLE IId. Univariate Analyses in Brothers (N = 133)

	Brothers of ADHD probands (N = 78)	Brothers of normal controls (N = 55)	*P* value
Extra help in school	41% (32)	29% (16)	0.20
Repeated grade in school	1% (1)	0% (0)	0.59
Special class in school	10% (8)	11% (6)	0.96
	Mean ± SD	Mean ± SD	
ADHD symptom score	3.9 ± 4.2	2.3 ± 2.9	0.05
Agoraphobia symptom score	0.16 ± 0.51	0.22 ± 0.41	0.11
Conduct disorder symptom score	1.0 ± 1.5	0.55 ± 1.2	0.03
Major depression symptom score	2.1 ± 3.0	1.4 ± 2.4	0.33
Separation anxiety symptom score	1.2 ± 1.5	0.69 ± 0.79	0.08
Simple phobia symptom score	1.4 ± 1.8	1.1 ± 1.7	0.40
Social phobia symptom score	0.78 ± 1.6	0.58 ± 1.2	0.57
Overanxious symptom score	1.6 ± 1.6	0.95 ± 1.3	0.01
Panic disorder symptom score	0.51 ± 1.8	0.27 ± 1.2	0.31
Cognitive summary score	−0.96 ± 3.7	1.2 ± 3.8	0.003
Current global assessment of functioning score	67.4 ± 10.6	70.1 ± 8.4	0.07
Past global assessment of functioning score	60.6 ± 11.8	66.0 ± 10.6	0.006
Socioeconomic status	1.8 ± 0.84	1.4 ± 0.63	0.002

explanatory variables that was entered into the stepwise logistic regression models. Mothers, fathers, sisters, and brothers were examined separately (Table IIa–d, respectively). A number of significant differences were seen between mothers of ADHD probands and mothers of normal controls (Table IIa). Compared with mothers of normal controls, mothers of ADHD probands had higher rates of extra help and repeated grades in school; they also had higher ADHD, conduct disorder, major depression, panic disorder, antisocial personality disorder, and generalized anxiety disorder symptom scores, lower current global assessment of functioning, past global assessment of functioning, cognitive, and socioeconomic status scores.

A number of significant differences were also found between fathers of ADHD probands and fathers of normal control probands (Table IIb). The fathers of ADHD probands had higher ADHD, conduct disorder, major depression, separation anxiety, and antisocial personality disorder symptom scores, lower cognitive, current and past global assessment of functioning scores, and lower socioeconomic status compared with fathers of normal controls.

Only two significant differences were found between sisters of ADHD probands and sisters of normal controls (Table IIc). Sisters of ADHD probands had higher ADHD and conduct disorder symptom scores than sisters of normal controls.

A number of significant differences were seen between brothers of ADHD probands and brothers of normal controls (Table IId). Brothers of ADHD probands had higher ADHD, conduct disorder, and overanxious disorder symptom scores, lower cognitive and past global assessment of functioning scores, and lower socioeconomic status than brothers of normal controls.

Table III presents the final logistic regression models in the relatives. Models were run separately in mothers, fathers, sisters, and brothers (Table IIIa–d, respectively). Although there was some overlap between the variables that were retained in each model, no two

TABLE III. Logistic Regression Models in Relatives

a. In mothers*

Variable	Odds ratio	Standard error	Z	*P* value
ADHD symptom score	1.21	0.09	2.5	0.012
Cognitive summary score	0.87	0.04	−2.9	0.003
Current global assessment of functioning score	0.95	0.02	−2.5	0.013
Generalized anxiety disorder symptom score	1.17	0.08	2.3	0.022

* Hosmer-Lemeshow goodness of fit test: $\chi^2 = 274.72$, $df = 244$, $P = 0.10$.

b. In fathers*

Variable	Odds ratio	Standard error	Z	*P* value
ADHD symptom score	1.20	0.06	3.5	0.001
Major depression symptom score	1.13	0.06	2.2	0.030
Socioeconomic status	1.54	0.34	2.0	0.047

* Hosmer-Lemeshow goodness of fit test: $\chi^2 = 118.40$, $df = 111$, $P = 0.30$.

c. In sisters*

Variable	Odds ratio	Standard error	Z	*P* value
ADHD symptom score	1.14	0.07	2.2	0.030

* Hosmer-Lemeshow goodness of fit test: $\chi^2 = 20.96$, $df = 13$, $P = 0.07$.

d. In brothers*

Variable	Odds ratio	Standard error	Z	*P* value
Cognitive summary score	0.86	0.04	−2.9	0.004
Past global assessment of functioning score	0.96	0.02	−2.4	0.018

* Hosmer-Lemeshow goodness of fit test: $\chi^2 = 132.99$, $df = 130$, $P = 0.41$.

models had exactly the same variables. For example, the logistic regression model discriminating mothers of ADHD probands from mothers of normal controls showed that the ADHD symptom score (i.e., number of ADHD symptoms that were endorsed), the cognitive summary score, the current global assessment of functioning score, and the generalized anxiety disorder symptom score were the variables in the profile that yielded the greatest discriminating ability (Table IIIa). Similarly, the logistic regression model in fathers also showed that the ADHD symptom score was an important characteristic in the profile that discriminated fathers of ADHD probands from fathers of normal control probands (Table IIIb). In contrast, the model in fathers showed that the major depression symptom score and socioeconomic status were also part of the discriminating profile, while the cognitive summary score, the current global assessment of functioning score, and the generalized anxiety disorder symptom score were not.

The logistic regression model in sisters was similar to the models seen in both parent groups in that the ADHD symptom score was an important characteristic in discriminating group status. In contrast to the models in parents, the profile that yielded the greatest discriminating ability in the sisters consisted of only that one variable (Table IIIc). The logistic regression model in the brothers differed from the models in all the other relative groups in that the ADHD symptom score was not part of the profile discriminating group status (Table IIId). Moreover, the profile in brothers included the past global assessment of functioning score, which was not seen in any other relative profiles. Similar to the model in mothers, the cognitive summary score was also an important characteristic of the profile in brothers.

The equivalence of these four logistic regression models was evaluated by comparing the sum of the likelihoods from the four separate models and the likelihood from the model examining all relatives at once. The results of this analysis yielded a $\chi^2 = 25.2$ on 21 degrees of freedom (df) ($P > 0.05$).

DISCUSSION

Using logistic regression models, we identified a quantitative phenotype in relatives that consists of measures across psychiatric, cognitive, and psychosocial domains. It is possible that psychiatric genetics may be better served by diagnostic constructs created for that particular intent than by existing diagnostic criteria that currently exist for broader purposes in clinical settings. The finding that so many of the univariate analyses were significant, especially in parents, is consistent with what we expected: that these features may reflect the phenomenology of an ADHD gene. However, there is a lot of redundancy among these features and therefore when they were entered simultaneously into a logistic regression model only some of them were retained.

The combination of these variables in a quantitative logistic regression model yielded a discriminating genetic phenotype for mothers of children with ADHD that included four variables: the ADHD symptom score,

the cognitive summary score, the current global assessment of functioning score, and the generalized anxiety symptom score. In contrast, the combination of these variables yielded a genetic phenotype for the fathers that included three variables: the ADHD symptom score, the major depression symptom score, and socioeconomic status. That cognitive scores were a significant discriminator in mothers but not in fathers is not surprising, since impaired cognitive functioning is more prevalent in males than females. This may be related to the tenet that males are more prone to central nervous system insults [Hynd and Semrud-Clikeman, 1989a,b; O'Callaghan et al., 1992]. Analogously, it is not surprising that the total number of major depression symptoms (summary score) was a significant discriminator in fathers but not in mothers, since major depression is estimated to be twice as prevalent in females than in males. The finding that socioeconomic status (SES) is retained in the father model may be indicative that SES is a correlate of the higher rates of psychopathology in fathers of ADHD probands. Alternatively, it could be indicative that SES is itself a causal factor. Further work is needed to determine the influence of SES. The differences between mothers and fathers highlight the importance of considering demographic factors such as gender and SES in the definition of familial phenotypes.

It is difficult to interpret the findings from the logistic regression model in sisters, since the model did not fit the data well (Hosmer-Lemeshow Goodness of Fit Test $\chi^2 = 20.96$, $df = 13$, $P = 0.07$). This poor fit suggests that the DSM-III-R categorical approach is superior in looking at the phenotype in sisters of probands with ADHD.

The combination of variables in brothers of children with ADHD yielded a genetic phenotype that included the following two variables: cognitive functioning summary score, and past global assessment of functioning score. The finding that the number of ADHD symptoms in boys was not part of the profile discriminating among brothers is at first glance puzzling. Although a significant difference in ADHD symptom score was observed between brothers of ADHD probands and brothers of normal control probands on a univariate level (odds ratio = 1.13, $P = 0.02$), the ADHD symptom score did not add any discriminating ability to the profile. This is probably due, in part, to the fact that ADHD was so prevalent in brothers of normal controls (9%). Moreover, the ADHD symptom score was significantly correlated with the past global assessment of functioning score (Spearman correlation coefficient = -0.52, $P = 0.0001$) and slightly correlated with cognitive functioning summary score (Spearman correlation coefficient = -0.16, $P = 0.07$).

The finding that the discriminating variables in the brothers were reflective of socioeconomic status is particularly interesting. Since these variables could be associated with all types of psychopathology they may not necessarily be useful in developing a discriminating genetic taxonomy for ADHD. The absence of SES differences in the sisters is consistent with existing literature suggesting that males (i.e., brothers) may be more affected by environmental factors such as perinatal complications while females (i.e., sisters) may represent a more genetic group. Additional study is needed in order to fully evaluate this hypothesis.

While our findings in the four groups of relatives suggest that we were successful in creating a quantitative phenotype in adults (i.e., mothers and fathers), our approach was not as useful in children (i.e., sisters and brothers). The fact that our approach did not improve the ability to discriminate among children is not surprising, since the diagnostic criteria have been designed for this age group and, in general, have been shown to be useful. While we believe our new quantitative phenotype in adults may be useful in the context of genetic analyses, we do not imply that such a nosology will be useful for clinicians or that it should replace DSM-III-R.

Our work must be interpreted in the context of its methodological limitations. An issue in this study is recall bias, which may be especially problematic in the assessment of childhood diagnoses in adult relatives, since it requires them to recall experiences from childhood. For example, the diagnosis of ADHD requires an onset of symptoms by age 7 years. Moreover, another limitation of our work is that the use of maternal reports to make diagnoses of children may have led to those diagnoses being influenced by maternal psychopathology. However, incorporation of maternal reports is standard clinical practice, since children are considered to be poor reporters of their symptoms [Achenbach et al., 1987].

Another potential limitation in clinical studies is Berkson's bias, i.e., the sample may include a misleadingly high proportion of subjects with multiple diagnoses just because referral will have been influenced by the occurrence of each separate condition [Berkson, 1946]. However, high levels of comorbidity have been observed in both clinical [Biederman et al., 1987, 1991a,b, 1992] and epidemiological samples [Anderson et al., 1987; Angold and Costello, 1993; Bird et al., 1988], suggesting that the high levels of comorbidity seen in clinical samples are not solely an artifact of Berkson's bias. Similarly, since 50% of the referrals to the Pediatric Psychopharmacology Unit at Massachusetts General Hospital have never been evaluated or treated, this sample does not have the severity bias that might be associated with a tertiary care facility. Since we did not control for age, and since the original sample of probands in this investigation came from clinical referrals, we do not know to what degree these findings will generalize to nonreferred populations in the community.

An additional potential shortcoming is that not all relatives were included in the analysis due to indirect interviewing (mostly of fathers) or inadequate data. The most extreme situation was the case of fathers of ADHD probands, where only 79% were available for inclusion in the analysis. However, as shown in Table I, no differences were noted in availability of subjects, whether they were a relative of an ADHD proband or a relative of a normal control.

Another pitfall of this investigation is that we were not able to determine whether the different predictive

models in the four groups of relatives were significantly different from one another. Although our statistical test comparing the four models did not reveal statistically significant differences, this could be due to insufficient power. Therefore, our conclusions can only be considered tentative. Further studies of larger size are needed before more definitive conclusions can be made.

A further limitation of this investigation is that our data can only demonstrate a familial association between the profile of characteristics in the relatives and ADHD in the proband. We infer that it is reasonable to use the familial form of ADHD as a proxy for the genetic form, since it is believed that genetic factors mediate the familial transmission of ADHD. However, studies of twin or adoption samples are needed to verify that genetic factors account for the familial transmission of the profile of characteristics seen in the relatives. Since we do not yet know the nature of true genetic cases, familial aggregation may be a reasonable standard for the development of phenotype definitions for use in genetic analyses [Blacker et al., 1993].

Another limitation is that by extending our phenotype definition to include anxiety in mothers and major depression in fathers, it is possible that the false-positive rate could have been increased. Moreover, the models used may be incorrect or based on erroneous assumptions. The model assumes that an ADHD genotype exists. Even if differences between relatives of ADHD probands and relatives of controls are found, other more complex genetic and environmental factors may be responsible for them [Blacker and Tsuang, 1993]. However, a phenotype definition based on these differences should still help eludicate features that suggest familial transmission, and might be of benefit in weighting the contribution of individual relatives in a linkage analysis.

Despite these limitations, our results suggest that the use of fitted logits (or predicted probabilities) may be valuable as a potential index of caseness for linkage studies. Since different characteristics were included in the different groups of relatives, our results are consistent with an existing body of literature [Anderson et al., 1987; Bird et al., 1988; Safer and Krager, 1988], and indicate that gender and generation (parent vs. sibling) may moderate expression of ADHD. Therefore, different phenotype definitions for each group of relatives may be necessary to delineate this variable expressivity.

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